

Methodological Challenges in Describing Medication Dosing Errors in Children

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Abstract

Although children are prescribed medications in 30 percent to 50 percent of clinic visits, little is known about medication errors in ambulatory pediatrics. In the process of completing a study to determine the prevalence of outpatient dosing errors, we identified a number of barriers to understanding the epidemiology of medication errors in children. These barriers include prescribing medication that is not labeled for use in children, discrepancies in published dosing recommendations for many medications, unclear guidelines on use of adult dosing recommendations for children of different ages and weights, and the lack of readily available documented weights to determine appropriate weight-based doses for children. In our study of pediatric medication errors, we found a wide range of doses prescribed to children for every medication we studied. Before we can truly understand medication errors in children and begin developing systems-based approaches to eliminating these errors, we need better national standards of medication doses that are appropriate for children and an improved ability to determine errors through databases that include children's weights as well as prescription information.

Background

Errors of medication use are among the most common types of medical errors and include mistakes of prescribing, dispensing, administering, or monitoring medications.^{1,2} Children visit the doctor an average of 1.8 times per year, and physicians prescribe medication during 30 percent to 50 percent of these encounters. In a recent survey of 1,600 American Academy of Pediatrics members, pediatricians reported writing prescriptions for 53 percent of patients seen during an average workweek. Among those prescriptions, 73 percent were for short-term acute illnesses, and 29 percent were for chronic long-term illnesses.³ Despite how frequently medications are prescribed in ambulatory settings, little is known about the frequency and types of medication errors that occur, the clinical importance of these errors, or effective strategies for error reduction.

Children are particularly vulnerable to medication dosing errors because of the unique circumstances involved in prescribing medication to children. In the ambulatory setting, several factors likely contribute to medication errors include the following: (1) an accurate weight must be obtained and correctly transcribed; (2) the health care provider may need to convert pounds to kilograms; (3) the

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health care provider must make rapid weight-based calculations for nearly every pediatric prescription he or she writes; (4) the correct preparation and concentration (liquid, chewables, tablets) of the medicine must be included in the dosage calculation; (5) the total daily dose may need to be divided into multiple doses to obtain the appropriate frequency for the medication; (6) communication with the parent or caregiver often will occur without the medication present; (7) the prescription must be legible and correctly interpreted by the pharmacist; and (8) the pharmacist must dispense the appropriate medication in its appropriate formulation labeled with the appropriate dose and frequency.

Tenfold dosing errors in children can easily occur due to a misplaced decimal point or a trailing zero.⁴⁻⁶ For example, a 1.0 mg dose may be misread as a 10 mg dose and not recognized as an error by a pharmacist because the 10 mg dose is still within the range of adult doses for the medication. In addition, health care providers must be aware of both the pediatric dosing recommendations (to calculate a weight-based dose in mg/kg/day) and adult dosing recommendations (to ensure they do not exceed the maximum recommended adult dose in mg/day). Furthermore, children cannot always communicate symptoms that may alert parents and providers to an adverse drug reaction if a medication overdose or underdose is taken by the patient.

More is known about medication errors in hospitalized patients than in the outpatient setting. Errors in medication ordering are the most common cause of preventable adverse drug events in hospitalized patients.^{1,7} In one adult study, half of all preventable adverse drug events occurred at the physician ordering stage, and the most common type of error was in medication dosing.¹ A study in a tertiary care hospital in New York demonstrated that medication dosing errors were the most common type of medication prescribing error, and these errors occurred at a higher rate in children than adults: 5.89 per 1,000 orders on the pediatric service, compared with 4.12 per 1,000 orders on the adult medical service.⁸ In a pharmacy-based review of medication orders in two pediatric hospitals, Folli et al.⁹ found that errors occurred in approximately 0.5 percent of medication orders, and the majority of errors were dosing errors. Children under the age of 2 years and pediatric intensive care unit patients were at highest risk. In the most comprehensive study involving pediatric patients, medication errors occurred in nearly 6 percent of all medication orders.⁷ Serious medication errors, those in which harm to the patient was possible, occurred at an alarming rate of 10 per 100 hospital admissions or 1 percent of all medication orders. Over half of these errors were dosing or frequency errors, and the physician ordering the medication committed the majority of these errors. Finally, in a retrospective study of medication errors reported to the U.S. Food and Drug Administration's Adverse Event Reporting System, administration of the wrong dose of medication was the most common type of error resulting in death.¹⁰

The Institute of Medicine (IOM) report on error in medicine identified computerization of medication prescribing as an important patient safety strategy.² Computerized order entry, combined with advanced decision support systems, has been shown to reduce prescribing errors in hospital settings across

many different drug classes.¹¹⁻¹⁵ Computerized order entry reduces medication errors by standardizing medication orders. Omissions of dose, route, and frequency are eliminated, as are errors from misinterpretation of illegible handwriting or use of nonstandard abbreviations. When coupled with computerized clinical decision support systems that provide feedback to the prescriber at the point of care, computerized prescription ordering has the potential to substantially reduce adverse drug events and improve patient safety.

The majority of outpatient settings do not currently use electronic prescription ordering or clinical decision support tools, and few studies have attempted to demonstrate the effectiveness of computerized prescription ordering on reducing medication errors and/or adverse drug events in ambulatory settings. Furthermore, there are many feasibility barriers that impede implementing these tools in outpatient practices outside of large hospital settings. These include the large financial resources necessary to implement computerized prescription ordering with decision support tools and the lack of support staff to train and maintain a system, if implemented.

Before the prevalence of dosing errors in ambulatory pediatrics can be studied, it is first necessary to clearly define exactly what a dosing error is. Although this task seems straightforward at first glance, many subtleties and challenges arose during the course of our studies. Specifically, we grappled with these following issues:

1. Off-label use of medication in children is common, particularly for psychotropic medications and other newer classes of medications. Many times, pediatric doses for these medications are difficult to find and may be extrapolated from adult doses with little scientific evidence to support safety and efficacy.
2. Published sources of pediatric dosing information differ in their recommendations for dosing ranges for children, sometimes by as much as a two-fold difference in the maximum recommended dose. Furthermore, ranges provided for weight-based dosing often encompass large ranges, sometimes as much as four-fold differences between the minimum recommended dose and the maximum recommended dose.
3. Indications for appropriate adult dosing is in total milligrams per day (mg/day) rather than in weight-based milligrams per kilogram per day (mg/kg/day), the system for indicating dosing for children.
4. Determining medication errors in children is only possible with accurately documented weight in kilograms.

This manuscript addresses in further detail the issues and challenges we faced in clearly understanding and defining dosing errors in the pediatric ambulatory setting.

Barriers to safe pediatric prescribing

Off-label use of medication in children

As many as 50–75 percent of prescription medications are labeled by the manufacturer as having insufficient information on pediatric use, particularly for young children and infants.¹⁶ In some newer drug classes, there are no medications licensed for use in children, leaving providers only the choice of prescribing a medication off-label or not prescribing. Safety concerns have been raised about medications used in children without adequate testing.¹⁷ For example, the selective serotonin reuptake inhibitors (SSRIs) have been associated with growth attenuation, an adverse effect not found in prelicensure studies in adults.¹⁸ Some SSRIs have also been associated with increased rates of suicidality for adolescents.¹⁹ Nonetheless, many medications are appropriately and frequently used in children, despite the lack of pediatric labeling.

When medications are prescribed to children off-label, providers often extrapolate pediatric doses from adult doses provided in published sources such as health plan formularies or MICROMEDEX[®].²⁰ Alternatively, they may rely on local expert opinion for pediatric dosing recommendations or obtain pediatric doses from published studies in the medical literature.

In our attempt to define overdoses and underdoses of medications to determine potential dosing errors, medications that were not approved for children, but were commonly used in children, were particularly problematic. For example, oxycodone is an analgesic that is not FDA-approved for use in children. However, because of this drug's ability to relieve pain, it is often used in children who do not respond to less potent pain medications. Oxycodone is a narcotic analgesic that, if inappropriately overdosed, could cause serious adverse effects, including depressed mental status, depressed respiratory drive, and potentially even death. We found the recommendations listed in Table 1 when attempting to determine appropriate dosing ranges for medication for use in children.

All of the sources in Table 1 are reliable, reputable sources for pediatric dosing of medications. However, a dose at the upper limit of appropriate for one

Table 1. Dosing information for oxycodone

| Source | Recommended pediatric dose* |
|--|---|
| <i>Harriet Lane Handbook</i> ¹⁹ | 0.2 to 0.9 mg/kg/day (0.05 to 0.15 mg/kg/dose q 4-6 hours). |
| Health Maintenance Organization's formulary | No weight-based dose provided. |
| MICROMEDEX ²⁰ | Safety and effectiveness not established in children. 0.2 to 0.9 mg/kg/day (0.05 to 0.15 mg/kg/dose q 4-6 hours). |
| Large regional children's hospital formulary | 0.2 to 1.6 mg/kg/day (0.05 mg/kg/dose q 4-6 hours to 0.2 mg/kg/dose q 3-4 hours). |

* More complete dosing information is available from each source.

source (a children's hospital formulary) would be considered nearly a twofold overdose by another source's dosing standards (*Harriet Lane Handbook*²¹).

Appropriate dosing of off-label medications can be further complicated by some sources recommending doses for children at the lower end of an acceptable adult dose. This is often a practical recommendation, as many medications licensed only for adult use do not come in liquid formulations, making accurate dosing of children more difficult. If liquid preparations are not commercially available, providers must dose in fractions of tablets ($\frac{1}{2}$ tablet, $\frac{1}{4}$ tablet). However, other sources may recommend weight-based dosing for these same medications. Before large scale systematic trials are completed and FDA labeling is provided for a medication, it is unclear which dose is most appropriate for children. For example, olanzapine is an antipsychotic medication that is not currently licensed for use in children under age 18 years. Table 2 represents different pediatric doses for olanzapine recommended in several selected sources.

Table 2. Dosing information for olanzapine

| Source | Recommended pediatric dose* |
|---|---|
| <i>Harriet Lane Handbook</i> ¹⁹ | Prepubescent: 2.5 mg/day. Adolescent: 5 mg/day. |
| Health Maintenance Organization's formulary | Adults > 18 years: 5–10 mg/day. No pediatric dosing recommendations provided. |
| MICROMEDEX ²⁰ | Safety and effectiveness in children not established. |
| Expert opinion (pharmacist from University of Massachusetts with expertise in psychopharmacology) | 0.1 to 0.7 mg/kg/day. |

* More complete dosing information is available from each source.

Again, an appropriate dose using one recommendation may result in an overdose or underdose using the other recommendation. In our study on pediatric dosing errors, for example, a 13 year-old child who weighed 80 kg was dispensed a prescription for olanzapine of 2.5 mg every day. If the child is considered prepubescent, then this dose is appropriate according to the *Harriet Lane Handbook*. However, the dose is 0.03 mg/kg/day, only 30 percent of the minimum weight-based dose recommended by an expert in pediatric psychopharmacology.

Researchers who are attempting to evaluate medication dosing errors often will not know which source the provider was using to determine an appropriate dose to prescribe to an individual child. This makes categorizing errors difficult. One solution is to allow the most liberal definition available (the widest range in dosing compiled from various sources). This would provide a conservative estimate of medication dosing error rates.

Discrepancies in dosing recommendations

The problem of conflicting dosing recommendations is not limited to off-label use in children. Commonly used medications also have different dosing recommendations. As an example, amoxicillin is the most commonly used medication in children. This one drug accounts for approximately 10 percent of all dispensings for children at one large health maintenance organization (HMO). Yet recommendations for appropriate dosing vary, depending on the source of information. Table 3 illustrates the wide variety of recommendations for amoxicillin.

Table 3. Dosing information for amoxicillin

| Source | Recommended pediatric dose* |
|--|---|
| <i>Harriet Lane Handbook</i> ¹⁹ | Standard dose: 25–50 mg/kg/day High dose: 80–90 mg/kg/day |
| Health Maintenance Organization's formulary | Standard dose: 30–50 mg/kg/day High dose: 80–100 mg/kg/day |
| MICROMEDEX ²⁰ | Standard dose: 25–50 mg/kg/day High dose: 80–90 mg/kg/day |
| Large regional children's hospital formulary | 25–50 mg/kg/day |

* More complete dosing information is available from each source.

Although there is less variation in the recommended doses for amoxicillin, there is still a 10 percent difference in the upper range of recommended appropriate doses when Group Health Cooperative's formulary and the *Harriet Lane Handbook* are compared (Table 3).

Furthermore, there is a wide range of acceptable doses. If a provider had meant to prescribe 25 mg/kg/day, but inadvertently calculated the dose based on pounds instead of kilograms (thereby prescribing 2.2 times more medication than he or she meant to prescribe), potentially no error would be detected because this dose would still fall well within the recommended range. While it may be unimportant from a clinical perspective to detect or prevent a child from receiving 55 mg/kg/day of amoxicillin instead of the intended 25 mg/kg/day, from a systems perspective this is a lost opportunity to identify a medication error. Such lost opportunities hamper steps to identify systemwide problems and may prevent detection of other, potentially more serious errors. If the same child returned with a broken arm and was prescribed codeine at the upper limit of an acceptable dose, but the provider again used pounds instead of kilograms to calculate the dose, this child may come to harm from a 2.2-fold overdose of a narcotic analgesic. Lack of standardization of weight-based dosing makes detection of many potential errors difficult if not impossible, allowing for missed opportunities for future error prevention strategies.

Adult dosing guidelines applied to children

It is often unclear when adult dosing guidelines should be followed. For example, the recommended dose of amoxicillin for children is between 25 and 90 mg/kg/day, with many guidelines recommending higher doses, given the increasing level of microbial resistance to the penicillins. However, many practitioners in our study of potential medication dosing errors began using the minimum adult dose of 750 mg/day for amoxicillin for children as young as age 5 years diagnosed with otitis media. In this instance, when a child weighs more than 31 kg, the 750 mg/day adult dose is less than the minimum weight-based dose for children (e.g., 25 mg/kg/day x 31 kg = 775 mg/day). This practice contributed to nearly 20 percent of amoxicillin doses in our study dispensed to children below the age of age 12 years being lower than the recommended weight-based dosing minimum.

Most medications have different recommended doses for children, often based on mg/kg/day, but very few medications have clear guidelines on which dose might be most appropriate for a given age. Children metabolize many drugs differently than adults and have different volumes of distribution for other medications. From a research perspective, defining an underdose of a medication is difficult if the dose is at least the minimum adult dose, as it is not clear which guideline a prescriber might have been using to determine the daily dose for a medication.

Deficient data on weights

Many medications that are used in children are most appropriately prescribed by calculating a weight-based dose in total milligrams per kilogram per day. In order to appropriately prescribe these medications, practitioners need an accurate weight, recorded either in kilograms (ideal) or in pounds, which can then be converted into kilograms. Ideally, weights would always be recorded in kilograms to avoid errors in converting pounds into kilograms when calculating medication doses; however, parents are often interested in their child's weight in pounds. In clinic visits, weights are therefore often measured and recorded in pounds in the medical record. Most retail pharmacies do not mandate inclusion of the child's weight on written prescriptions. Therefore, it is difficult for pharmacies to correctly determine if a weight-based dosing error has occurred.

Researchers or quality assurance members of a health plan attempting to retrospectively evaluate appropriateness of doses of medications likewise must rely on accurate weights. Their task may be even more difficult, because they must rely on documented weights and have no real way of knowing whether a documented weight reflects the weight of the patient at the date of the prescription. A provider could potentially recognize a pound-to-kilogram conversion error or inaccurate weight by noting that a child visually appeared more than or less than the recorded weight.

Although many health care systems are moving toward electronic medical records (EMRs), most do not currently have readily available weights in their

administrative data sources. In our efforts to study medication dosing errors in children in 10 HMOs nationally, only 2 had available weights for children along with their pharmacy claims data for the years 1999–2001. Most organizations had only the amount of medication dispensed and the days supply. This is insufficient information to evaluate potential medication dosing errors in children for two primary reasons. First, there is tremendous variation in normal weights for young children; therefore, extrapolation of a weight is likely to be inaccurate. Second, many children are dispensed medication in liquid formulations, which makes determining the amount dispensed to be taken daily potentially inaccurate. A child may be prescribed an antibiotic to be taken 5 ml 3 times per day for 10 days (150 ml total), but be dispensed a 200 ml bottle of medicine with instructions to discard the remainder. The automated data will reflect that a 200 ml bottle was dispensed, but not the amount prescribed. If the investigator was to attempt to determine the daily dose from a 10-day supply, he or she would mistakenly conclude the child was prescribed 20 ml per day (200 ml/10-day supply). An alternative source of data would be to use the “sig” or directions for use. However, these data are often difficult to retrieve electronically, and even when available require manual interpretation.

Health care systems that are interested in monitoring appropriateness of pediatric medication doses need electronic accurate weights for rapid assessment of appropriateness of medication doses dispensed to young children. Similarly, researchers with access to large health organizations’ pharmacy data can only readily evaluate medication dosing errors in children if either the database contains access to an EMR with weights available, or weights are routinely documented in the medical chart and there are sufficient funds and staff available to conduct medical record reviews. In our study of dosing errors, the site with an EMR had documented weights available for greater than 94 percent of the patients selected for the study. In comparison, a documented weight was available only 80 percent of the time in medical records for the sites using paper charts. Although large pharmacy chains often contain complete records of medications dispensed to children, they do not routinely require weights or record weights if provided. Therefore, opportunities to study medication dosing errors in large pharmacy databases from these sources are limited.

Conclusions

Although medications are prescribed to millions of children each year in the United States, very little information is available on the epidemiology of medication errors that occur in the ambulatory setting. Children are particularly vulnerable to medication dosing errors because of the relatively complicated process of calculating and then prescribing appropriate medication doses for them. Researchers and policymakers interested in studying medication dosing errors in children should be aware of the many barriers to defining errors in the pediatric population.

First, lack of evidence to support age-appropriate dosing parameters in many medications, particularly medications not licensed for use in children, results in a wide range of published recommendations. Discrepancies exist in published recommendations for many medications, both labeled and off-label for children. This makes defining an appropriate dosing range, and thereby defining underdoses and overdoses, problematic. This is a critical limitation to accurately ascertaining and describing medication dosing errors.

Second, the wide range of acceptable weight-based doses makes standardization difficult. This is also a barrier to identifying potential errors that may be “hidden” within a large acceptable dosing range. In retrospective studies, it is difficult to know the dose a health care provider intended to prescribe to a child. It is far easier to quantify the appropriateness of the dose a child is dispensed. With wide dosing ranges allowable for each weight, prescriber calculation errors and other arithmetic errors may be undercounted.

Third, for many medications that are commonly used in both children and adults, it is unclear when it is appropriate to switch from a weight-based pediatric dose to an adult based mg/day dosing regimen. Many minimum recommended adult doses fall well below the minimum recommended weight-based dose for school-aged children. Although we know that children metabolize many medications differently than adults, we do not currently have published information on when a provider should use adult doses over pediatric doses of medications (or vice versa). In our study, we defined an underdose of a medication as a medication dispensed below both the adult minimum recommended mg/day and the pediatric minimum mg/kg/day. If we had only looked for errors in weight-based dosing regimens for children as young as age 4 or 5, we would have overcounted underdoses for many medications, especially psychotropic medications and antibiotics.

Finally, existing data sources from which medication error detection is possible often lack the necessary elements, including weights and complete prescription information, to accurately describe errors without a formal, costly chart review. More detailed data sources are needed to appropriately target interventions to reduce outpatient medication errors in children.

Children are frequently exposed to prescription drugs. It is imperative that we gain a better understanding of the risk factors for medication errors and how to effectively prevent medication errors from occurring. Many of the barriers to accurately describing the magnitude of the problem exist because of lack of standardized evidence-based information about appropriate use of therapeutics in children. Our work highlights the need to fund and undertake research that can illuminate the critical area of dosing in pediatric medicine to ensure safe use of medication in this vulnerable population.

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